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By W. B. CANNON and HENRY LYMAN.

[From the Laboratory of Physiology in the Harvard Medical School.[

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THE DEPRESSOR EFFECT OF ADRENALIN ON ARTERIAL PRESSURE.

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In 1911, during an investigation of the effect of splanchnic stimulation on the fatigue of skeletal muscle,[1] a rise of blood pressure, followed by a fall and a later rise, was repeatedly noticed while the nerves were being excited (see Fig. 1, *A*). Since the object of the investigation was to determine whether secretion from the adrenal glands influenced muscular fatigue, elimination of the direct vascular effects of splanchnic stimulation became necessary. Accordingly the cœliac axis, the superior and inferior mesenteric and the renal arteries were tied, and the experiment was then repeated. Splanchnic stimulation now caused an almost or quite sheer fall of pressure (see Fig. 1, *B*). This fall was obtained repeatedly under the conditions above described; it occurred after all nervous connections with the aorta and inferior vena cava had been excluded, and furthermore it occurred after direct stimulation of one of the adrenal glands. It seemed, therefore, that in the cat, the animal used in these observations, a substance was produced by the adrenal glands which caused a pure fall of blood pressure.

Previous Observations of a Depressor Effect of Adrenalin.

Scattered through the literature on the adrenal glands can be found references to a depressor effect on arterial tension produced by adrenal extract or adrenalin itself. Bardier and Fränkel in 1899 observed that in two instances injection of adrenal extract induced a vasodilation in kidneys and spleen as shown by oncometer regis-

[1] Cannon and Nice: this Journal, 1912, xxix, p. xxiv.

tration.[2] In 1900 Moore and Purington reported that extracts of adrenal medulla of the ox caused, when given in exceedingly minute doses, a fall of blood pressure in the dog. Larger doses resulted in the typical rise of pressure. They suggested that the extract might contain two substances, the depressor substance stronger because effective at greater dilution; but they also admitted that a single substance might be present having opposite effects according to its dosage.[3] These observations have been variously explained away. Pari found in a few instances an increased flow through the perfused kidneys and hind legs of dogs when a weak adrenalin solution kept for some time was added to the circulating fluid, but this did not occur if the adrenalin solution was fresh. He expressed the belief, therefore, that adrenalin, even in very small doses, never causes (in rabbits) a fall of arterial pressure, and he suggested that the results obtained by Moore and Purington were due to chemical changes in the dilute extracts used by them.[4] Vincent has intimated that in these and in other instances of a depressor constituent of the adrenal glands[5] the common power of tissue extracts to lower blood pressure may be invoked in explanation.[6] Thus doubt is thrown on

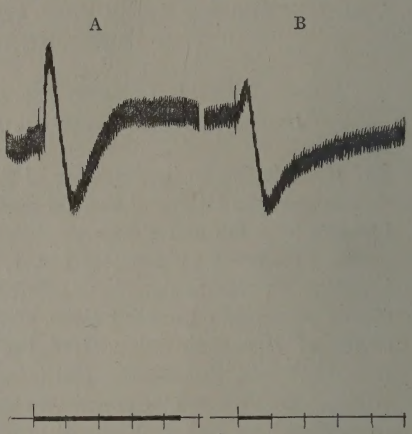

FIGURE 1. — *A*, blood-pressure changes during stimulation of left splanchnic nerves two and one-quarter minutes. *B*, the same, after tying arteries of the splanchnic area; stimulation, half a minute.

[2] BARDIER and FRÄNKEL: Journal de physiologie et pathologie générale, 1899, i, p. 960.

[3] MOORE and PURINGTON: Archiv für die gesammte Physiologie, 1900, lxxxi, p. 483.

[4] PARI: Archives italiennes de biologie, 1906, xlvi, p. 218.

[5] See GÜRBER: Sitzungsberichte der physikalisch-medicinischen Gesellschaft, Würzburg, 1897, iv, p. 54; HUNT: this Journal, 1900, iii, p. xviii.

[6] VINCENT: Internal secretion and the ductless glands, London, 1912, p. 174.

the validity of the inference that adrenalin in tissue extracts can lessen arterial tension.

Results concordant with those recorded by Moore and Purington, however, have been noted by persons who have employed not adrenal extracts, but pure adrenalin. Thus S. J. and C. Meltzer reported, within three years after Moore and Purington's observation, that subcutaneous injection of adrenalin caused dilation of the blood vessels of the rabbit's ear in normal conditions, but constriction if the nerves to the vessels were cut.[7] In his summary of the action of adrenalin (1905), Elliott stated that he had seen extraordinarily dilute solutions of adrenalin cause a lowering of blood pressure in the cat, but that solutions of 1: 600,000 or 1: 200,000, if "slowly and exactly made," produce only rise of blood pressure.[8] "Straightforward experiment," Elliott declared, "fails to prove vascular dilation by adrenalin." By previously injecting active preparations of ergot, however, Dale showed that adrenalin could cause a marked fall, due to vasodilation. The discussion of this result will be deferred till later; for the present the fact need only be noted that, after injections of ergotoxine, adrenalin becomes a pure depressant, even in large doses.[9] Further evidence that ergotoxine is not necessary for this effect was brought forward last year by Hoskins and McClure, who demonstrated that the fall of blood pressure in dogs, noted by Moore and Purington, was as true for minute doses of adrenalin as for minute doses of adrenal extract.[10] And Elliott has recently examined the reason for failure to secure an even rise of pressure during excitation of the splanchnic nerves. He has noted that the disturbance (a drop) in the curve coincides with signs of adrenalin being freed in the body (dilation of the pupil), and has shown that in the absence of the adrenal glands the effect can be similated by injecting adrenalin during splanchnic stimulation.[11] All these observations taken together indicate that adrenalin does

[7] Meltzer, S. J. and C: this Journal, 1903, ix, p. 261.

[8] Elliott (Journal of physiology, 1905, xxxii, p. 411) did not mention the dosage or the rate of injection when these solutions raised the pressure, and both are important factors.

[9] Dale: Journal of physiology, 1905, xxxii, p. lix; 1906, xxxiv, p. 169.

[10] Hoskins and McClure: Archives of internal medicine, 1912, x, p. 353.

[11] Elliott: Journal of physiology, 1912, xliv, p. 405.

not always increase arterial tension, but, in small doses, may indeed lower the tension. The almost direct fall in the blood pressure record reproduced in Fig. 1, *B* is therefore due to the liberation of adrenalin from the adrenal glands when the splanchnic nerves are stimulated.

In spite of the foregoing evidence the idea is firmly fixed that adrenalin is normally an agent raising blood pressure by vaso-constriction. For example, Biedl, in his summary of the literature on the ductless glands, describes, as the most important and most characteristic of the physiological effects of adrenalin, its action in raising blood pressure, and although mentioning the secondary fall observed in some animals states that the rise occurs even with minimal doses.[12] Vincent likewise has testified that although he has frequently employed very small doses, he has never seen the depressor effect of adrenal extract.[13]

The Objects and Methods of the Present Investigation.

An investigation of the depressor action of adrenalin is important for several reasons. As already shown, the adrenal secretion poured out in the first moments of stimulation of splanchnic nerves causes blood pressure to fall. Depression due to adrenalin may therefore be a common phenomenon in conditions affecting these nerves, as strong sensory stimuli, pain, and major emotional states. Furthermore, the widespread conception that adrenalin is strictly vasopressor in action warrants a consideration of its depressor function. And, finally, because adrenalin mimics the sympathetic system, which is usually regarded as vasopressor, the vasodepressor action should be carefully considered. For these reasons the investigation here reported was undertaken.

Although Meltzer observed vasodilation of the rabbit's ear after a small subcutaneous injection of adrenalin, we have not been able to produce in the rabbit a fall of blood pressure with any dose, even the most attenuated. We have found no reference in the literature

[12] Biedl: Innere Sekretion, Berlin and Vienna, 1913, second edition, i, pp. 429–430.

[13] Vincent: *Loc. cit.*, p. 174.

to a depressor action of adrenalin in the rabbit, and, according to Dale, the rabbit is exceptional in not showing a reversal of the pressor effect of adrenalin after ergotoxine. Hoskins and McClure showed that the dog might be used for the study. Because in the cat, however, the depressor action of splanchnic and adrenal stimulation was first seen by us, that animal was selected for the present investigation.

In order to produce uniform and readily repeated effects the adrenalin must be newly prepared, must not deteriorate during the course of the experiment, must be administered in carefully measured amount and at a carefully regulated rate. The preparation used was that made by Parke, Davis & Co., and was fresh. Immediately before the experiment it was diluted, usually 1: 100,000, with distilled water, in which the adrenalin remains without chemical change much longer than in salt solutions. The injections were made into an external jugular vein, low in the neck, from a syringe with small barrel, graduated to tenths and fiftieths of a cubic centimetre. A sound which could be clearly heard recurring at intervals of one second permitted delivery of the dose uniformly in successive experiments. Thus it was possible to give .02 c.c. at the rate of .01 c.c. per second or 1 c.c. at the rate of 0.1 c.c. per second, or any intermediate combination of amount and rate of injection that was desired, and this could be repeated with satisfactory accuracy.

Usually the animals were anæsthetized with urethane. Since there is some relation between urethane anæsthesia and the efficacy of adrenalin,[14] ether was used in some instances, and in others the cerebrum was destroyed during brief ether anæsthesia and the tests then tried on the decerebrate animal. The means of securing anæsthesia did not alter the effects of adrenalin, however, and consequently urethane (2 gm. per kilo, by stomach) was selected, both for its convenience and for its even action.

Blood pressure was registered by means of a mercury manometer connected with either a femoral or a carotid artery. In many instances the abdominal aorta, the subclavians and carotids were tied, thus limiting the circulation largely to thorax and abdomen. The pressure was then registered from one of the carotids. In all in-

[14] See UNDERHILL: Journal of biological chemistry, 1911, ix, p. 13.

stances both vagus nerves were severed. An electric heating pad placed under the animal permitted the maintenance of normal temperature.

Conditions for the Depressor Effect of Adrenalin.

As shown in Fig. 2, a series of doses, varying from .3 c.c. to .05 c.c., of an adrenalin solution 1: 100,000, injected each at the rate of

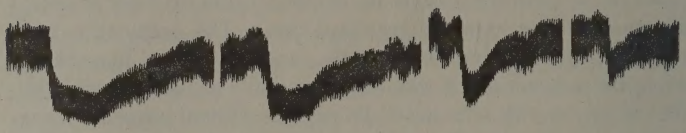

Figure 2. — Graded drops in blood pressure, with graded doses of adrenalin, 1: 100,000 (.3, .2, .1, and .05 c.c.) given at the rate of .01 c.c. per second. Time, half-minutes.

.01 c.c. per second, results in a series of drops in blood pressure, graded in accordance with the dose. Much more than .3 c.c. can be given at the rate of .01 c.c. per second — several cubic centimetres, in fact — without causing anything but a depression in the curve. In this connection the conclusion of Hoskins and McClure [15] that the adrenals do not ordinarily produce sufficient secretion to affect the sympathetic system is eminently justified, for even when extra secretion is provoked by splanchnic stimulation the amount liberated at first is of the order demonstrated in Figs. 1 and 2, and in the cat, at least, reduces blood pressure rather than raises it.

The same amount will have different effects according to the rate

[15] Hoskins and McClure: *Loc. cit.*, pp. 352, 353.

of injection. Thus .5 c.c. (1: 100,000) given slowly (.02 c.c. per second) results in a pure fall of pressure, and given more rapidly (.1 c.c. per second) results in a primary rise followed by a fall (see Fig. 7, last two doses). Similarly, increasing doses of a strong solution (*e. g.*, 1 : 10,000), injected at a uniform rate, evoke progressively changing effects — varying from a pure fall to a rise followed by an almost equal drop below the original level, and finally to an almost pure rise, with relatively little subsequent drop (see Fig. 3).[16]

Repeated doses of an amount which evokes a fall of pressure act additively to evoke a further fall. As shown in Fig. 4, however, the degree of effect soon reaches a maximum. After the pressure had fallen from approximately 160 mm. to 136 mm., further injections lowered it no more. The injection of .4 c.c. (1: 100,000) in the same case — .1 c.c. at the rate of .01 c.c. per second, followed continuously by .1 c.c. at the rate of .02 c.c. per second, and that by .2 c.c. at the rate of .1 c.c. per second (see Fig. 5) — also reduced the pressure from 166 mm. to 136 mm. A similar result is seen in Fig. 2; .3 c.c. in that instance caused no further drop than .2 c.c., but the effect was more lasting. Of course, small doses do not lower the pressure

[16] In a recent paper (Journal of industrial and engineering chemistry, 1912, iv, p. 636) WEIDLEIN, like PARI, has drawn the conclusion that the depressant property of epinephrin is due to impurities present in the gland and to decomposition products formed by oxidation. His evidence for this conclusion is, that with his repurified epinephrin, lowering of arterial pressure did not occur after the initial rise; whereas, with commercial or decomposed epinephrin, the initial rise was not so high and the subsequent depression was marked. WEIDLEIN used very strong doses — 1 c.c. of 1: 10,000 in most instances, *i. e.*, from fifty to one hundred times the physiological doses used by us. It is quite possible that the depression became marked as his solutions deteriorated because the epinephrin injected in 1 c.c. was thus reduced to a more nearly physiological amount. We have in fact obtained a direct drop in blood pressure by use of the very pure ash-free epinephrin refined by TAVAU (see Bulletin No. 55, Hygienic Laboratory, U. S. Public Health Service, 1909, p. 23), which was kindly provided by Dr. REID HUNT. Furthermore, we have obtained a direct drop in blood pressure with .2 c.c. of fresh colorless commercial adrenalin (1: 100,000), and then placed the solution in a warm bath in the sun for fifteen minutes, when it turned pink. Now the same dose (.2 c.c.) still caused a fall of blood pressure, but no greater fall than before. The solution was again exposed to the sun for fifteen minutes and was changed to a much deeper pink. Now the same dose had no effect whatever upon blood pressure, and even when 5 c.c. were introduced failed to cause a drop. As the material decomposed, therefore, it became not depressant but inert.

as much as large doses, but, on the other hand, the depressive power is limited, and the limit may still leave the pressure at a high level.

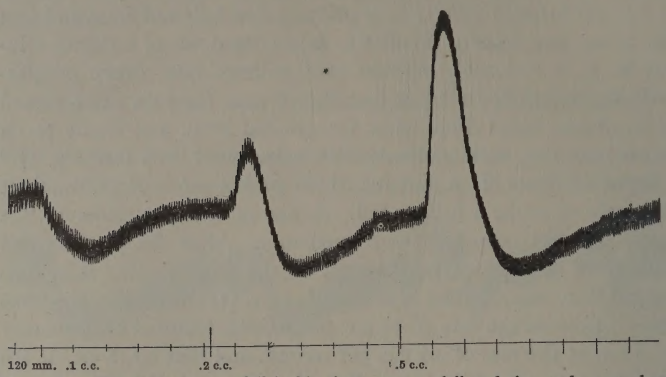

FIGURE 3. — Change from pure fall in blood pressure to fall and rise, and to predominant rise, with increasing doses (.1 c.c., .2 c.c., and .5 c.c.) of adrenalin 1:10,000. Time line, 120 mm. Hg; time, half-minutes.

The percentage fall has varied, for doses of .5 c.c. (1:100,000), between 13 and 22 per cent; and in a given case the percentages have been fairly constant at different initial pressures. Thus in three distinct cases the figures were as follows when a maximum straight drop [17] resulted from a single dose:

Original pressure. mm.	Drop. mm.	Percentage drop.
150	34	22
136	30	22
162	34	21
116	26	22
160	24	15
150	20	13
162	24	15
146	20	14
164	32	19
180	34	18

[17] Usually the drop produced by a dose that causes a slight rise at first, is greater than one not preceded by the rise. In one such case the drop amounted to 54 mm.

In one instance, after the subclavian and carotid arteries and the abdominal aorta below the kidneys had been tied, and the left adrenal gland excluded, arterial tension was registered at 80 mm. Now .1 c.c. adrenalin (1:100,000), injected .02 c.c. per second, lowered the tension 22 mm. The left splanchnic nerve was then stimulated and the tension thereby increased to 118 mm. The same dose as before, introduced during the stimulation, lowered the pressure 32 mm. In the first condition the percentage drop was 27.5, in the second 28. It appears, therefore, that the ratio of fall to initial pressure is fairly constant in a given case, and with arterial tensions of medium value.

If the arterial tension is lowered, however, by compression of the heart through the thoracic wall, or by placing clips on the portal and inferior caval veins, the percentages vary widely from what is average under more normal conditions. The pressure may be thus lowered mechanically to 70 or 80 mm. of mercury. A dose of adrenalin (.5 c.c., 1:100,000) then causes the pressure to fall still further — in one case 10–12 mm., *i. e.*, about 15 per cent. In this animal the pressures ranged normally between 116 and 162, and the percentage fall, with the same dose, was about 22 (see first group of figures, p. 383).

The Depressor Effect of Adrenalin Due to Vasodilation.

Examination of the arterial pressure curve registered on a rapid drum reveals no noteworthy alteration of the heart rate, and only slight diminution of the pulse pressure as the drop occurs. A straight drop of 42 mm. in 38 seconds was produced by injecting .1 c.c. adrenalin (1:100,000) in 1 second, and even with this marked and rapid fall the heart showed no change of beat. The fall, therefore, probably results from lessened peripheral resistance due to vasodilation. This inference we have justified by showing that an increase in the volume of a hind-leg occurs at the same time with the lowering of blood pressure. The inference is also supported by Dale's observation that the depressor effect of adrenalin after ergotoxine is accompanied by increased volume of parts.

Because of evidence of vasodilator nerves in the head and limbs the question arose as to whether the depressor effect resulted from

vasodilation exclusively in these parts of the body. Accordingly, after tying the internal iliac arteries, clips were placed on both subclavians, both carotids and the left iliac (the pressure was being registered from the right femoral). The pressure rose from 154 mm. to 190 mm. A dose of adrenalin (.5 c.c., 1: 100,000) now caused a fall of 12 mm. The clips were removed and the pressure fell to 146 mm. The same dose now lowered the pressure by 22 mm. Next the inferior mesenteric artery was tied, and clips were placed on the superior mesenteric and renal arteries and on the cœliac axis. The pressure rose to 166 mm., and the dose, again repeated, caused a fall of 18 mm. Thus the vasodilation is not confined to any one field of the body, but affects alike the outlying limbs and the splanchnic area.

The character of the drop in pressure suggests that the adrenalin may affect the vasoconstrictor centre as the depressor nerve affects it — thus being able to replace impulses at one point in the central nervous system just as it may replace them in organs supplied by sympathetic fibres. In one instance only in our series did adrenalin wholly fail to induce a pure fall of pressure; by good fortune the depressor nerve was separate in this animal, and when stimulated induced a marked drop in the curve. Adrenalin probably does not, therefore, act like impulses delivered by the depressor nerve.

Conditions Changing the Depressor into a Pressor Effect.

As already stated, weak solutions of adrenalin injected more and more rapidly, or stronger solutions injected at a uniform rate but in gradually larger doses, are followed progressively first by a fall of pressure, then by a rise and fall, and finally by almost a pure rise. Thus the amount introduced in a given time is capable of changing the depressor into a pressor effect. But other conditions can be demonstrated which are favorable to this reversal, with no change in the rate of injection.

1. **Reversal after pithing.** — Pithing the brain and upper spinal cord was performed through an opening in the orbit. After this operation the blood pressure usually falls to about 50 mm. of mercury. As the fall is occurring, and immediately after a level is reached, the

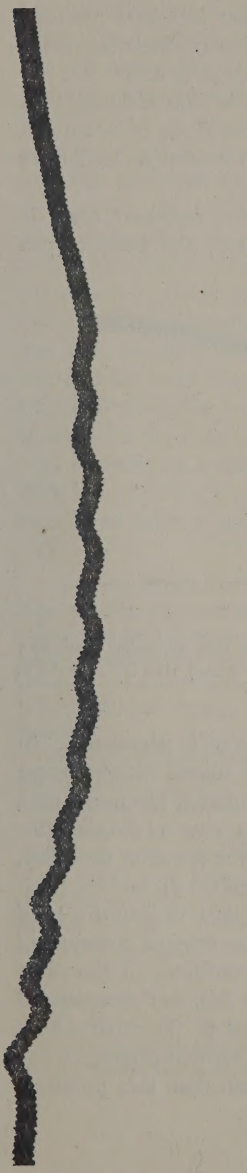

FIGURE 4. — Gradually lower drop in blood pressure with repeated doses of adrenalin, each .1 c.c., 1:100,000, given at the rate of .02 c.c. per second. Time line, 80 mm. Hg.; time, half-minutes.

adrenalin dose which was effective before has, in some of our cases, failed to produce any change. This insensitiveness, when present, soon disappears, and then the dose which previous to the pithing caused a pure drop in the curve now causes a pure rise (see Fig. 6, *A*, *z*, before pithing; and *B*, after pithing) — there has been an exact reversal of results.

Observations made before and after pithing show that the latent period, measured between the beginning of the injection and the beginning of the fall or rise, is approximately the same for the two effects. On one occasion, however, the rise appeared after seven seconds, whereas the fall was never seen in less than ten seconds after the adrenalin began to be introduced.

The rise after pithing is not due to any changed action on the heart, for a record made on a rapid drum shows no alteration of the rate of beat adequate to explain the new effect. The elevation of pressure, therefore, results from increased peripheral resistance — pithing has transformed the vasodilator action of adrenalin to a vasoconstrictor action.

The fact that adrenalin alone may thus have opposite effects rules out the first of Moore and Purington's suggestions, namely, that there might be two substances acting oppositely — one to reduce,

the other to raise blood pressure. The further fact here recorded rules out the necessity of their second suggestion (a single substance opposite in action according to dosage), for opposite effects are observed with the same dosage. The problem is thus reduced to a question of what reverses the effect of uniform doses of adrenalin. Before considering that question further, other conditions leading to reversal will be described.

2. **Reversal during depressor stimulation.** — If the depressor nerve is stimulated and adrenalin is then administered, the pressure can

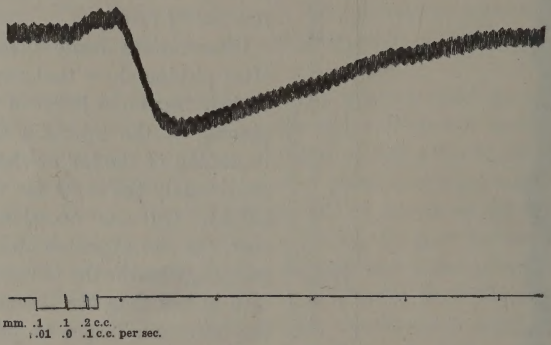

FIGURE 5. — Same case as Fig. 4. Drop in blood pressure after adrenalin, 1:100,000; .1 c.c. at .01 c.c. per second, then .1 c.c. at .02 c.c. per second, then .2 c.c. at .1 c.c. per second.

be made to fall further than if the depressor alone is stimulated. In Fig. 6, *A* is presented a record, taken from an animal with limb and carotid arteries tied, in which depressor stimulation alone caused a drop of 34 mm. Two doses of adrenalin (.2 c.c., 1:100,000) injected at the rate of .02 c.c. per second were given one after the other, while the stimulation of the depressor continued (to *y*), and the pressure was let down 40 mm. further. A third dose produced a brief rise followed by a drop of 10 mm. more. The original pressure of 184 mm. was thus reduced to 100 mm. Repetitions of the same dose of adrenalin now caused, not a further fall, but *elevations* of pressure; and when the pressure was restored to the original level the dose again caused a fall. In other words, without pithing or any other disturbance of the central nervous system than that produced

by stimulation of the depressor nerve, the effect of a small dose of adrenalin can be precisely reversed.[18]

3. **Effect of nitrites on the reversal.** — The ability of nitrites to lower blood pressure by action on peripheral structures is well known. If a small dose of nitroglycerine is given intravenously, the pressure falls, and then a dose of adrenalin that ordinarily produces a considerable reduction has no effect. As soon, however, as the change wrought by the nitrites is nearly past, and the former pressure is being recovered, the adrenalin again is able to exert a depressor action (see Fig. 7). After pithing, when all doses of adrenalin, even the minutest, cause an elevation of blood pressure, nitroglycerine is still capable of lowering it. Once when, after pithing, the pressure was only 26 mm., nitroglycerine caused a clearly marked further fall, and the least effective dose of adrenalin resulted in a rise. The failure of adrenalin to lower pressure after pithing is, therefore, not because the limits of vasodilation have been reached.

4. **Reversing the reversal by means of ergotoxine.** — As already stated, Dale has proved that, after pithing the brain and giving ergotoxine, even large doses of adrenalin cause a fall of pressure. The depres-

[18] In this instance the failure of the pressure to rise after the first and second doses of adrenalin, as it rose again at *z*, may be regarded as due to absence of vasoconstrictor impulses, because of continued stimulation of the depressor nerve. When the tone had been further lost, however, after the third dose, the action of adrenalin became reversed. Evidently the tone may be considerably reduced without reversal, and yet a critical point is reached at which reversal occurs.

The oscillations following adrenalin dosage (see Fig. 6, *A*) have often been noted; they may indicate the operation of opposite factors working on the vascular wall and tending towards equilibrium.

In a few instances reversal has been observed during the high pressure that prevails for a short period after the brain is pithed. The brief sustained tone of the blood vessels under these circumstances may be due to temporary excitation of spinal centres by the trauma above, for the fall caused by adrenalin is followed by a rise. As the general blood pressure gradually drops, a level is soon reached, however, at which adrenalin evokes a rise instead of a fall.

On warming an animal to 44° C. the pressure fell from 150 mm. to 100 mm., and the adrenalin dose that produced a fall at normal temperature then produced a rise. Possibly in this case the result should not be attributed primarily to the effect of heat on the smooth muscle of the vessel walls, but to injury of the central nervous system and consequent loss of vascular tone.

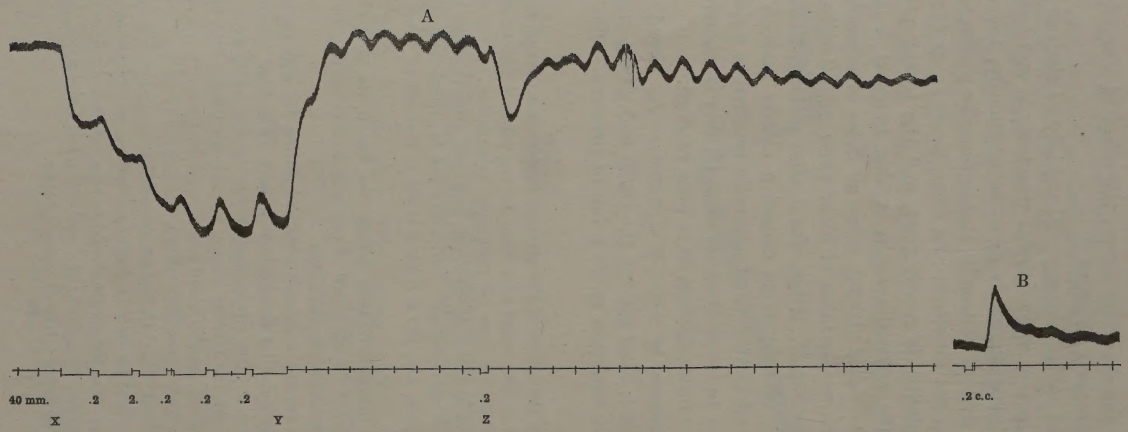

FIGURE 6.—Seven tenths the original size. *A*, successive drops in blood pressure during depressor stimulation (*x* to *y*) and with first three doses of adrenalin (1: 100,000), then reversal of effect with last two doses. After pressure restored pure drop in pressure with same dose. Time line, 40 mm. Hg. *B*, same animal, after pithing down to mid-thorax. Rise of pressure with same dose as before. Time line, 40 mm. In every instance the dose was .2 c.c., given .02 c.c. per second.

sive action of adrenalin lost after pithing can be restored by ergotoxine with no change of dose.

In one case (that described on p. 387 and represented in Fig. 6), while the pressure was at 104 mm., .2 c.c. of adrenalin (1:100,000), given at the rate of .02 c.c. per second, caused a fall of 34 mm. (Fig. 6, *A*, *z*). The brain, and the cord as far as the mid-thorax, were pithed,

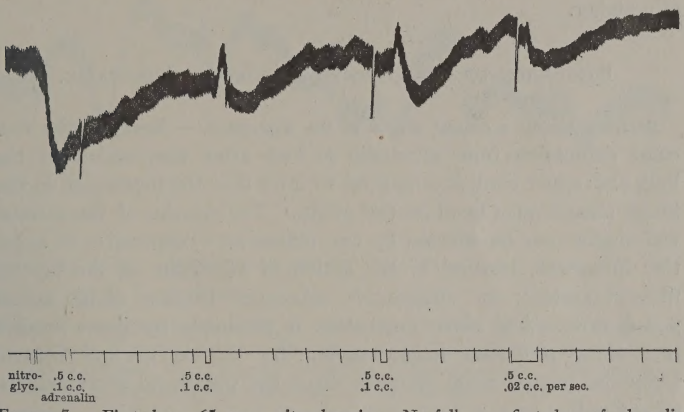

FIGURE 7. — First dose, .65 mgm. nitroglycerine. No fall from first dose of adrenalin given during nitroglycerine depression. Rise and fall after second and third doses adrenalin (1:100,000), .5 c.c., .1 c.c. per second. Pure fall after fourth dose, .5 c.c., .02 c.c. per second. Time, half-minutes.

and then, with the pressure at 50 mm., the same dose produced a rise of 26 mm. (see Fig. 6, *B*). The entire cord was now pithed and yet, by means of repeated doses of ergotoxine (.65 mgm. in each), the pressure was increased to 132 mm. Stimulation of the left splanchnic nerves, and injection of the same dose of adrenalin as before, each resulted in a marked fall of pressure. Three minutes later splanchnic stimulation caused, after a slight fall, a rise of 22 mm.; and when, during continuance of the stimulation, the same dose of adrenalin was repeated, a straight drop of 24 mm. occurred, and later 14 mm. more (see Fig. 8).

Evidently in the foregoing instance, in the complete absence of the central nervous system, the ability of a small dose of adrenalin to lower blood pressure was quite restored by giving ergotoxine.

This restoration is not the result of merely increasing the pressure. When that is done (after the pressure has once fallen in a pithed

animal), either by further pithing of the upper cord, or by injecting stronger solutions of adrenalin than those used in this investigation, or by stimulating the splanchnic nerves (after limb and neck vessels are tied), pressures from 140 mm. to 180 mm. can be temporarily produced. But doses of adrenalin which usually lower the pressure either have no effect under these circumstances or raise the pressure still higher.

Discussion of the Opposed Actions of Adrenalin.

Evidence against a central source of the depression. — Because the vascular depression from adrenalin is lost after destruction of the bulb and upper cord, it is natural to infer that the depression in the intact animal must be of central origin. The muscles of the arterial wall might thus be affected by two influences — depressive or negative influences, because of the action of adrenalin on the central nervous system; and stimulative influences, because of its action peripherally. And since depression is produced by doses weaker than those producing augmentation, the central nervous control would be proved more sensitive than the peripheral structures to adrenalin.[19]

Adrenalin might indeed act centrally to cause vasodilation, by stimulating the known vasodilators to the limbs[20] and head, but this possibility is rendered improbable by continuance of a marked depressor effect after all limb and head arteries are tied (see p. 385). Or adrenalin might lower pressure by inhibiting the tone of the vasomotor centre; but when that centre is in a tonic state and capable of being inhibited, as shown by action of the depressor nerve, adrenalin may fail to have any effect whatever (see p. 385). The assumption that the fall of blood pressure is of central origin meets another difficulty in accounting for the marked drop in pressure after ergotoxine, in an animal with the entire cord wholly functionless from pithing (see Fig. 8, *A*). The central nervous system, therefore, is not needed to explain vasodilation after adrenalin, and the evidence does not support the view that vasodilation is normally of central origin.

[19] See Meltzer, S. J. and C.: *Loc. cit.*, p. 259.

[20] See Bayliss: Journal of physiology, 1902, xxviii, p. 298.

Evidence against depression being due to blocking of vasoconstrictor impulses by adrenalin. — While arteries are connected with the central nervous system they are continually receiving impulses, which hold their muscular walls in tonic contraction against the internal pressure. Vasodilation under these circumstances might be due to

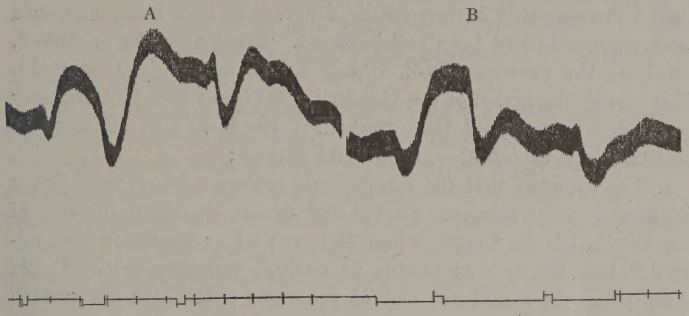

FIGURE 8. — A continuation of Fig. 6; blood pressure raised by ergotoxine. *A*, first rise from .65 mgm. ergotoxine; first fall from stimulation of left splanchnic nerves; second fall from .2 c.c. adrenalin (1:100,000), .02 c.c. per second. *B* (three minutes later), rise from splanchnic stimulation (*x* to *y*); two doses of adrenalin, each .2 c.c., .02 c.c. per second, cause fall. Time line, 40 mm. Hg; time, half-minutes.

a blocking of vasoconstrictor impulses. Thus, indeed, adrenalin might act. And certainly while pressure is high from stimulation of splanchnic nerves (in an animal with limb and neck vessels tied), the drop resulting from a small dose of adrenalin (see p. 384) strongly gives the impression that the splanchnic impulses are being blocked. But if that is the action of adrenalin, why does it not produce the same result when splanchnic nerves are stimulated after pithing or the pressure is raised by further destruction of the spinal cord? Under these circumstances the temporary rise is due to constrictor impulses delivered to the vessels, and yet, as already stated, adrenalin causes not a fall, but may cause an additional rise.

The drop of pressure from adrenalin after ergotoxine has been given to an animal with the cord entirely destroyed (see p. 390) is also inconsistent with the view that the drop results from the blocking of impulses, for the central nervous system has been abolished. This view, therefore, may properly be regarded as having little support.

Are the opposed effects of adrenalin due to stimulation of vasoconstrictor and vasodilator nerve endings? — If the depressor effect of adrenalin is not due to change in the central nervous system or to the blocking of vasomotor impulses from the spinal cord, the effect must be wrought in the muscle fibres themselves. This is the view which Dale has supported in accounting for vasodilation from adrenalin after ergotoxine had been administered. Ergotoxine, he explained, paralyzes the vasoconstrictor endings in the muscle, and adrenalin then reveals the action of the vasodilator endings which had formerly been overwhelmed and thus masked.[21] We have had difficulty in accepting this explanation, for several reasons:

1. The evidence that the sympathetic system conveys vasodilator impulses is very meagre. Dastre and Morat described dilation of the vessels of the tongue when the cervical sympathetic was excited,[22] but Elliott was unable to confirm the observation.[23] On stimulating the peripheral end of the right splanchnic nerve with break shocks at the rate of one in a second or one in two seconds, Bradford observed marked expansion of the kidney with either no change of blood pressure or a slight fall.[24] This result does not prove the distribution of peripheral dilators to the vessels of the splanchnic area in general, for the impulses that relaxed the kidney often did not equally affect the blood pressure. Also, from what is now known of the effects of adrenal secretion, the case of simultaneous dilation and drop in pressure might have resulted from liberated adrenalin — and this may have been a common source of error in other judgments of blood-pressure changes after splanchnic stimulation. Furthermore, even if vasodilator nerves are granted, Bradford's result does not prove that the dilation of the kidney was due to sympathetic impulses. Indeed Bayliss has explained instances of visceral dilation on the basis of his studies of dilation of limb vessels, as evoked by antidromic conduction in nerves of the dorsal roots.[25]

2. The known and well-established vasodilator nerves (apart from the dorsal roots of spinal nerves) do not belong to the thoracico-lumbar

[21] Dale: *Loc. cit.*, p. 201.

[22] Dastre and Morat: Comptes rendus, Académie des Sciences, Paris, 1880, p. 393.

[23] Elliott: Journal of physiology, 1905, xxxii, p. 411.

[24] Bradford: *Ibid.*, 1889, x, p. 387.

[25] Bayliss: *Loc. cit.*, p. 280.

(sympathetic) division of the autonomic system, but to the cranial and sacral divisions. In vessels and in other structures where fibres from the middle division meet fibres from either of the terminal divisions, the two are set in opposition. The opposition, in other words, lies not within the sympathetic, but between the sympathetic and the upper or lower group of autonomic nerves. And the action on arterial walls which the sympathetic opposes to these nerves is invariably constriction.

3. Adrenalin, as Elliott has shown, acts as if it stimulated sympathetic endings, or the myoneural junctions between sympathetic neurones and smooth muscle fibres. If the fall of blood pressure after small doses of adrenalin is due to stimulation of sympathetic endings, there must be vasodilator nerves in the sympathetic; but, as already explained, no well-supported evidence for the existence of such nerves in the sympathetic has been brought forward, and the assumption of their existence there contravenes the strongly established theory of the organization of the autonomic system. Furthermore, if weak doses of adrenalin stimulate vasodilator and strong doses vasoconstrictor endings, weak stimuli applied to splanchnic nerves might be expected to cause vasodilation and strong stimuli the opposite. This, however, is not true. After restricting the circulation to thorax and abdomen and tying off the left adrenal gland, we stimulated the left splanchnic nerves with electrical stimuli of various rates per second, and of various strengths — down to and below the threshold for any change whatever — and never obtained any other result than increase of blood pressure. The nerve impulses did not act, therefore, as they should have acted if weak adrenalin stimulates vasodilator endings.

4. Since weak electrical stimulation fails to support the view that weak adrenalin acts on vasodilator endings, there remains the possible application of Dale's suggestion — that adrenalin lowers blood pressure after ergotoxine because the latter paralyzes vasoconstrictor endings and leaves dilator endings still sensitive. This explanation applied to the observations recorded in the present paper involves assuming that vasoconstrictor endings are less sensitive than dilator endings normally, that pithing somehow renders the constrictor endings as sensitive as the dilator endings were before and wholly paralyzes the dilator endings, and that when ergotoxine is given and the

vessels are constricted, the constrictor endings are paralyzed, and the dilator endings are rendered sensitive again. Although there appears to be no good reason for excluding the possibility of this sequence of profound changes, yet so many ill-supported assumptions are involved, including the existence of sympathetic vasodilators, that it has seemed to us highly unsatisfactory.

Because the evidence for vasodilator nerves in the sympathetic system is slight; because the existence of such nerves, opposed to vasoconstrictor nerves in the same system, would not harmonize with the known organization of the autonomic system; because the depressor action of weak adrenalin described in this paper cannot be duplicated by weak stimulation of nerves to blood vessels; and because the reversed action of adrenalin here described involves assumptions as to effects on hypothetical nerve endings that seem to us unwarranted — for these reasons we are inclined to reject the view that adrenalin in small amount or after ergotoxine stimulates vasodilator nerves.

Does adrenalin act oppositely according to the state of the muscle? — The evidence thus far adduced has led us, by exclusion, to look for an explanation of the reversed action of adrenalin in the state of the muscle, for, after all, the primary observation on which this investigation was based was vasodilation when adrenalin was administered to vessels in high tonic contraction, and vasoconstriction when in a relatively atonic state.

Observations that the same agent applied to smooth muscle may have quite different effects according to the condition of the muscle have not been rare. Lepine noted that sciatic stimulation resulted in vasodilation if a leg is cooled, and in vasoconstriction if it is warmed.[26] Stewart observed that stimulation of the sacral nerves resulted in relaxation if the bladder was contracted, and in contraction if the bladder was relaxed.[27] Dale found that adrenalin caused relaxation of the non-pregnant uterus, but contraction of the pregnant.[28] Hooker has recently reported that carbon dioxide when applied to smooth muscle of the intestine causes it to relax if it is contracted and rhythmic, and to contract if relaxed and arhythmic.[29]

[26] Lepine: Mémoires, Société de Biologie, 1876, p. 26.
[27] Stewart: this Journal, 1899, ii, p. 192.
[28] Dale: *Loc. cit.*, p. 189.
[29] Hooker: this Journal, 1912, xxxi, p. 53.

Vasodilation, when vessels are still receiving tonic impulses from the central nervous system, or when, after denervation, they have been brought into sustained contraction by ergotoxine; and, on the other hand, *vasoconstriction*, after the vessels have been heated to 44° C., after they have lost their tonic contraction by being separated from the central nervous system, or have been largely deprived of tonic impulses by extreme action of the depressor nerve — these two effects of adrenalin we would place with the other foregoing examples of change in opposite directions, produced by a single agent, acting on smooth muscle under different conditions.[30]

To turn a group of results thus into the murky realm of smooth-muscle physiology for explanation is, of course, giving no explanation at all. In the presence of so much obscurity we hesitate to speculate as to the manner in which the opposite actions of adrenalin occur, and yet an hypothesis may be entertained if it is made to keep its proper place. On these terms we suggest the following possible way of regarding the phenomena described in this paper:

Contraction and relaxation, while separable processes, are directly and intimately related. The contracted muscle is prepared for relaxation, the relaxed muscle is prepared for contraction. Indeed, as a muscle is contracting it may become the seat of changes which, being incomplete, are unstable, and on being completed cause relaxation. Thus, for example, the contractile process might be due to partial oxidation; and the relaxation process might result from the further or total oxidation of the partly oxidized materials. Both contraction and relaxation could then be accounted for by a single procedure — that of oxidizing certain material in the muscle.[31]

In this view sustained contraction, or tonus, might be due to continuous production of partly oxidized materials at such rate that in spite of continuous further combustion they are present in excess. Under these circumstances any agent that would favor combustion might have two effects: by increasing the incompletely burned

[30] Dale has dismissed this explanation of the reversal of effect of adrenalin on blood pressure after ergotoxine because vascular tone may be lowered by large doses of ergot, and yet adrenalin causes relaxation. As shown in Fig. 6, *A*, however, lowering of the tone does not result in reversal unless a certain critical stage has been reached.

[31] *Cf.* Meigs: Journal of experimental zoölogy, 1912, xiii, p. 548.

materials it would increase contraction, by burning the excess of those materials it would cause relaxation. In a weak form the agent might affect the terminal phase, in a strong form it might affect in greater degree the initial phase.

In the state of total relaxation the material used for contraction may be regarded as being undisturbed. The only change that can occur first now, when the muscle is stimulated, is such partial combustion as will result in contraction. And in the absence of anything to continue the incomplete burning, the partial process will go on promptly to completion, and relaxation will attend it.

Without doing violence to the relation of adrenalin to the sympathetic innervation of blood vessels, it is possible by such a scheme to conceive the various shifting effects of adrenalin described in this paper. Adrenalin mimics the sympathetic system in starting the contractile process. The relaxation process, however, may be regarded as merely another stage of the same change, not different in kind; and we may suppose that under certain circumstances sympathetic impulses and their substitute, adrenalin, are capable of affecting that also. Thus the vasopressor effect of adrenalin, the vasodepressor effect, the drop after ergotoxine both when the splanchnic is stimulated and when adrenalin is given, and even the failure of adrenalin to cause a fall when in a pithed animal pressure has been raised by nervous stimulation or by strong adrenalin — can, we think, have a possible, though very hypothetical, explanation. But at the present stage of our knowledge the detailed application of this hypothesis to every phenomenon above reported as resulting from adrenalin dosage seems not worth while.

Summary.

Stimulation of an adrenal gland, or splanchnic stimulation after excluding splanchnic vessels, results in the cat in a fall of blood pressure due to vasodilation.

Injection of small doses of adrenalin (*e. g.*, .1 to .5 c.c, 1 : 100,000) at a uniform slow rate (*e. g.*, .02 c.c. per second), into a cat, causes a similar fall of blood pressure. This effect varies, within limits, with the dose and with the rate of injection. Repeated doses

causing vasodilation have a cumulative effect. The percentage drop in a given case is usually constant for the same dose, given at different initial pressures.

The depressor effect of adrenalin is changed into a pressor effect after pithing and after extreme depression from depressor stimulation combined with repeated relaxing doses of adrenalin. During the drop in pressure after pithing the brain the action of adrenalin may reverse from depressor to pressor. It reverses with high temperature (44° C.).

The depressor effect does not occur if arterial tension has been much lowered by nitroglycerine.

The reversal from depressor to pressor action after pithing can be again reversed to depressor action by ergotoxine (Dale).

Reasons are given for inferring that the depressor effect is not of central origin, is not due to blocking of vasoconstrictor impulses, or to stimulation of supposed vasodilator sympathetic endings by adrenalin.

The two effects, vasodilation and vasoconstriction, are attributed to opposite actions of adrenalin according to the state of the muscle — relaxation when tonically shortened, contraction when relaxed. Other instances of like character are cited.

A tentative hypothesis is offered to account for the opposite actions.

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